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VENTILATORY ACCLIMATIZATION TO HIGH ALTITUDE IS PREVENTED BY CO--ETC(U)
JUL 79 J C CRUZ, J T REEVES, R F GROVER PHS-HL-14985
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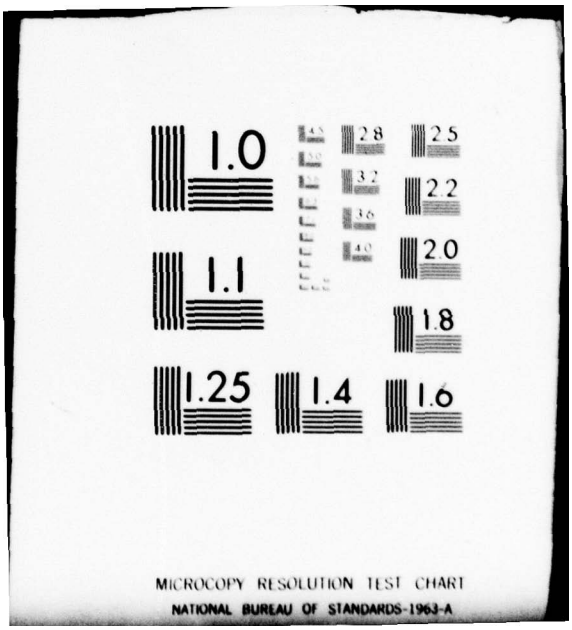
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VENTILATORY ACCLIMATIZATION TO HIGH ALTITUDE IS PREVENTED BY CO_2 BREATHING

J. C. Cruz, J. T. Reeves, R. F. Grover, J. T. Maher, R. E. McCullough, A. Cymerman and J. C. Denniston

Running Head: Alkalosis in Ventilatory Adjustments to High Altitude

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Cardiovascular Pulmonary Research Laboratory
University of Colorado Medical Center
Denver, CO 80262

and

United States Army Research Institute of Environmental Medicine
Natick, MA 01760

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ABSTRACT

The hypoxia of high altitude stimulates ventilation. If the resultant respiratory alkalosis inhibits the initial increase in ventilation, then with prevention of alkalosis, ventilation should rise immediately to a stable plateau. Four subjects inspired CO_2 (3.77%) from ambient air in a hypobaric chamber (P_{atB} = 440-455 torr) during 100 hours at high altitude. Ventilation (for given oxygen uptakes at rest and during exercise) increased promptly and remained stable. Four control subjects exposed to high altitude without CO_2 supplementation showed the expected progressive increases in ventilation with time. The hyperoxic CO_2 ventilatory response curve shifted progressively to the left with time in the control subjects but not in those given supplemental CO_2. The latter group also failed to increase the ventilatory response to isocapnic hypoxia. Thus, CO_2 supplementation at high altitude prevented the so called "ventilatory acclimatization" from occurring. Prevention of respiratory alkalosis at high altitude probably permitted maintenance of (H^+) at some central nervous system locus, thus allowing an uninhibited hypoxic stimulation of ventilation.

INTRODUCTION

Ventilatory acclimatization to high altitude is considered to be a progressive decrease with time in arterial CO_2 tension ($PaCO_2$), i.e. a progressive increase in alveolar ventilation (Kellogg, 1963, 1977). A progressive left shift of the curve that relates ventilation-$PaCO_2$ under hyperoxic conditions is also used to quantitate ventilatory acclimatization to high altitude (Mines and Sorensen, 1970).

When man goes to high altitude, several days are required to effect the full increase in ventilation, probably because the initial uncompensated respiratory alkalosis inhibits the hypoxic stimulation of ventilation (Eger et al., 1968; Kellogg, 1953, 1964, 1977; Kellogg et al., 1957). We reasoned that prevention of respiratory alkalosis by giving CO_2 to breathe during several days at high altitude should permit the ventilation to rise promptly to a relatively stable plateau. Eger et al. (1968) have shown that the administration of supplemental CO_2 during eight hours of hypoxia reduced almost to 50% a shift in the CO_2 ventilatory response curve. The utilization of CO_2 supplementation to prevent respiratory alkalosis during several days at high altitude has not previously been reported.

The purpose of the present study was to prevent respiratory alkalosis by CO_2 supplementation at high altitude and to test the hypothesis that the hypoxic stimulus to ventilation would thereby be unopposed. We planned to measure ventilation at rest and during exercise in relation to oxygen uptake, as well as ventilatory responses to isocapnic hypoxia and hyperoxic CO_2 stimulation. Potentially, such a study would be complicated by the fact that exposure to a given altitude would not provide the same degree of hypoxemia for hypocapnic and normocapnic subjects because of the "altitude

lowering" effect of CO_2 (McFarland and Dill, 1938; Rahn and Otis, 1947). Therefore, it was decided to pursue the study by exposing two groups of volunteers to equivalent degrees of alveolar hypoxia irrespective of altitude. We would attempt to maintain normocapnia in one group and allow the other to become hypocapnic. Although technical and theoretical difficulties were anticipated, the experiment seemed worthwhile in separating the hypoxic stimulation of ventilation from the inhibition of ventilatory stimuli by respiratory alkalosis.

METHODS

General Plan and Description of Subjects

Of the ten subjects participating in this study, seven were volunteer enlisted men from the United States Army Test Subject Platoon at the United States Army Research Institute of Environmental Medicine (USARIEM) at Natick, Mass. and three were members of the Special Forces. They varied in age from 18 to 22 years (mean 20 years), in height from 140 to 188 cm (mean 177 cm), in weight from 61.4 to 112.3 kg (mean 75.8 kg), and in surface area from 1.76 to 2.35 m^2 (mean 2.19 m^2). The subjects were divided into two groups of five, such that they had similar mean body weights and similar values of maximum oxygen uptake per kg of body weight. The aim for the first group of subjects (CO_2 group) during 100 hours at simulated high altitude was to maintain normocapnia at rest while the alveolar oxygen tension fell to a level between 55 and 60 mm Hg. The second group, designated as the group without CO_2, was to be exposed without CO_2 addition to an altitude which would match the alveolar oxygen tension in the CO_2 group. One subject in the group without CO_2 voluntarily withdrew from the study after 24 hours in the altitude chamber. Satisfactory ventilatory measurements

could not be obtained in one subject of the CO_2 group. Therefore, four subjects for each group are reported. Informed consent was obtained. The subjects cheerfully tolerated the rather prolonged confinement and were cooperative in every way. No ill effects attributable to the study were observed.

Conduct of the Experiment

The experiment was conducted in the hypobaric environmental chamber of the USARIEM. During the first two weeks the studies were carried out with the door of the chamber open to ambient sea level pressure, during which time the subjects were familiarized with the equipment and the experimental procedures. Morning control measurements were made of resting minute ventilation and end tidal O_2 and CO_2 gas tensions, followed by ventilatory response to hypoxia and hypercapnia. Oxygen uptake, minute ventilation and heart rate were measured at rest and during five minutes of upright bicycle exercise in the afternoon. The subjects exercised at 300 kilogram-meters per minute (kg-m/min) for five minutes and then, without rest, at 600 kg-m/min for a further five minutes.

At 7:00 AM, beginning the third week, the men in the CO_2 group entered the chamber which had been evacuated to a pressure of 465 mm Hg (altitude equivalent to approximately 4100 m). On arrival at high altitude and each morning thereafter up to 75 hours as specified in Table 1, seated subjects had measurements of end tidal O_2 and CO_2 tensions and ventilatory responses to isocapnic hypoxia and hypercapnia. The ambient carbon dioxide concentration of 3.77 $\pm$ 0.02% (SEM) was then maintained throughout the altitude study. The ambient temperature was 20° C and the relative humidity was maintained at 35%. After the measurements at 27 hours of exposure the

alveolar oxygen tensions were higher than the desired range and the pressure within the chamber was lowered to 440 mm Hg (altitude approximately 4600 m). In the afternoons at the times specified in Table 2, measurements of oxygen uptake, ventilation and heart rate were made with the subjects at sitting, rest, and during bicycle exercise at 300 and 600 kg-m/min. After the measurements had been concluded on the last day the subjects were dismissed.

At 7:00 AM, beginning the fourth week, the group without CO_2 entered the chamber at a barometric pressure of 492 mm Hg (altitude approximately 3600 m). No CO_2 was added. The temperature was 20° C and the relative humidity was 35%. Because the alveolar oxygen tension tended to rise with time due to the so called "ventilatory acclimatization to high altitude" the pressure within the chamber was lowered to 475 mm Hg after 55 hours. The schedule of measurements within the chamber was the same as with the CO_2 group.

Measurements

The instruments utilized for ventilatory measurements consisted of NOVA 1200 computer (Data General Corporation), an oxygen fuel cell (Weil et al., 1967), an infrared CO_2 analyzer (Beckman, model LB-1), a thermocouple anemometer for expired air flow velocity measurements (Technology Incorporated, model MFG-20H), a high velocity valve (Hans Rudolph) and, on the expired limb, a 5-liter mixing chamber with an internal electric fan to insure adequate mixing. For measurement of oxygen uptake the oxygen and CO_2 analyzers sampled the air in the mixing chamber and the anemometer measured the expired air velocity. The outputs from the analyzers plus that from the anemometer were fed into the computer which printed out

the ventilation, gas concentrations and calculated O_2 uptake as averaged values for successive 30-second intervals. Prior to measurements in each subject the oxygen and CO_2 analyzers were calibrated from gas tanks of known composition and inspired air was analyzed for oxygen and CO_2. At each altitude, and usually for each subject, the expired volume measured by the anemometer and computer was compared to that simultaneously collected in a Douglas bag measured with a Tissot spirometer. Analysis of the expired air within the bag allowed for frequent checks of the validity of oxygen uptake by the computer system. Alveolar air analysis was obtained by constantly withdrawing air from the dead space of the Rudolph valve at 100 ml/min through the O_2 and CO_2 analyzers. Ventilatory responsiveness to progressive isocapnic hypoxia was made following the technique of Weil et al. (1970). Ventilation was measured continuously over a period of 8 to 10 minutes as the alveolar PO_2 fell from 130 to 40 torr. Alveolar PCO_2 was held constant at the resting levels by adding CO_2 to the inspired gas. The magnitude of the response to hypoxia was judged by the parameter A, which describes the shape of the hyperbolic relationship of ventilation and P_AO_2 (Weil et al., 1970). The ventilatory responsiveness to progressive hypercapnia under normoxic conditions (P_AO_2 approximately 120 torr) was measured by the rebreathing method of Read (1967). The magnitude of the response to hypercapnia was judged by the slope (S) of the line relating ventilation to P_ACO_2. The intercept of the line extrapolated to 0 ventilation, the parameter B of Lloyd et al. (1958) was used to measure the shift of the line.

Statistical Analysis

Group differences were measured with a t-test and changes within a group were measured by an analysis of variance. Mean differences with a probability of 0.05 or less were considered significant.

Facilities

The altitude chamber consisted of two rooms connected by an air lock. One room, 6.3 m x 3.0 m x 2.5 m, housed all scientific equipment and one bed. The other room, 3.7 m x 2.8 m x 2.5 m, was living space utilized by the subjects. These were connected by the air lock, 2.2 m x 2.8 m x 2.5 m, and were operated as a single unit except when the air lock was opened to allow entry or egress. The chamber operation, including observation of the subjects, was carried out by a three-man crew which changed every eight hours. In addition, an Army medical officer remained continuously on-call and in the building while the chamber was in operation.

RESULTS

Alveolar PO_2 and PCO_2 at Rest at High Altitude, Table 1

The mean alveolar oxygen (P_AO_2) tensions at high altitude ranged from 55 to 62 mmHg in the CO_2 group and from 55 to 61 mmH_g in the group without CO_2. As intended, there were no significant differences in P_AO_2 between the groups. In the CO_2 group at high altitude the alveolar CO_2 tensions were maintained slightly above the sea level value, preventing hypocapnia. In contrast, hypocapnia developed in the group without CO_2.

Ventilation at Rest, Figure 1.

Resting ventilation measured in the morning showed a sharp increase in the CO_2 group at 3 h. of altitude exposure. No significant changes were observed thereafter. Analysis of variance showed that the four measurements carried out at high altitude were different from the sea level control. Subjects without CO_2 showed a progressive increase in ventilation with time. Differences in ventilation between the two groups were measured at 27 and 51 hours at high altitude ($P<.05$).

Ventilation During Exercise, Table 2

In both groups the oxygen uptakes measured at high altitude tended to be higher than those at sea level. No significant differences were observed in oxygen uptake between the two groups either at sea level or at high altitude. Oxygen uptake for a given work load did not vary significantly with time of altitude exposure.

Ventilations were higher at altitude than at sea level in both groups during exercise. However, ventilation changes with time of altitude exposure were different between the two groups. A progressive increase was observed in the control group while no significant differences were measured in the CO_2 group.

Ventilation at a Given Oxygen Uptake

It was necessary to examine the changes in ventilation without the interference of variations in oxygen uptake (for a given exercise load) at the various times. For the three metabolic levels examined the oxygen uptakes in Table 2 appeared to be near 500, 1000, and 1500 ml/min, for sitting rest and the two exercise stints, respectively. Therefore, the ventilation versus oxygen uptake was plotted for each subject on each day and values of ventilation were interpolated for oxygen uptakes at 500, 1000, and 1500 ml/min. The results shown graphically by work load (Fig. 2) indicated that the subjects with CO_2 supplementation had an abrupt increase in ventilation at high altitude, whereas those without CO_2 showed a progressive increase in ventilation throughout the altitude exposure.

Control of Breathing, Figure 3

No significant changes in the ventilatory response to isocapnic hypoxia were measured in the CO_2 group. On the other hand, an increase was observed at 75 hours in the group without CO_2 (Fig. 3, top).

Analysis of variance revealed no changes with time in the slope(s) of the ventilatory response to hypercapnia at high altitude for either the CO_2 group or for the group without CO_2 (Fig. 3, middle). On the other hand, the intercept of the line that relates $\dot{V}_E$ to P_{CO_2} (intercept B) showed no change in the CO_2 group. However, a progressive shift to the left occurred in the group without CO_2. The value at 75 hours at high altitude was different from the value at 3 hours (Fig. 3, bottom). There was a difference between the two groups during the last measurement at high altitude ($P<.01$).

DISCUSSION

The present study attempted to compare ventilatory adaptations in normal subjects who developed hypocapnia during several days at high altitude with those in whom the development of hypocapnia was prevented. To prevent hypocapnia we added CO_2 to the altitude chamber and analyzed the end tidal gas as a guide to CO_2 supplementation. Although hypocapnia was prevented, slight hypercapnia, relative to sea level, was produced during the first 51 hours of altitude exposure. By comparison, the group without CO_2 developed hypocapnia, such that differences between the groups were observed in end tidal CO_2 values. Arterial blood gases taken at the end of the altitude exposure and reported elsewhere (Grover et al., 1976), showed the same P_{CO_2} trends as did the end tidal values, although the arterial values were lower, probably due to excitement. The difference in ventilatory adjustments to high altitude observed between the two groups are considered in terms of a) patterns of total ventilation, b) ventilatory responses to CO_2 stimulation, and c) ventilatory responses to isocapnic hypoxia.

a) Patterns of Total Ventilation

The ventilatory responses to high altitude differed between the groups. Subjects without CO_2 addition showed a progressive increase in ventilation with time of exposure, whereas subjects with CO_2 supplementation showed an initial rise in ventilation to a value which remained essentially unchanged for the remainder of the altitude stay. The differences between the groups could not be explained by different degrees of alveolar hypoxia in keeping with experimental design nor by differences in metabolic rates. Also, the different patterns were consistent, being observed at rest in both the morning and the afternoon measurements and during two standard grades of exercise. Most of the ventilatory adaptation to high altitude in the group without CO_2 should have been accomplished during four days at high altitude and it is of interest that by this time the measured ventilations at rest and during exercise were equivalent in the two groups. Presumably the usual respiratory alkalosis of high altitude exposure did not occur with CO_2 supplementation, with the consequence that the hypoxic peripheral chemoreceptor stimulation of ventilation, unopposed by alkalosis, could immediately achieve a higher stable value. Thus, the supplemental CO_2 prevented the ventilatory acclimatization process that normally occurs on high altitude exposure.

b) Ventilatory Responses to CO_2 Stimulation

The changes in ventilation discussed above were accompanied by a progressive shift to a lower P_{CO_2} of the curve that relates ventilation to P_{CO_2} in the group without CO_2. In contrast, in the group with CO_2 added, the stable ventilation was characterized by an unchanged ventilation-P_{CO_2}

relationship. We quantitated the position of the relationship at the X-axis intercept of the extrapolated line relating ventilation to end tidal P_{CO_2}, the parameter "B" of Lloyd et al. (1958). Because our ventilatory responses to CO_2 were performed under hyperoxic conditions and the slope of the lin' 'id not change significantly with time, the B parameter appeared an adequate indicator of the shift in the ventilation-CO_2 relationship. Indeed, B parameter is used to indicate shifts by the Oxford group (Cunningham et al., 1961). It has been suggested that the shift in the relationship is a better indicator of ventilatory acclimatization to high altitude than $P_{A_{CO_2}}$ (Mines and Sorensen, 1970). However, "B" and $P_{A_{CO_2}}$ are well correlated, Fig. 4, suggesting that either measurement describes the acclimatization process. Eger, et al. (1968) gave CO_2 supplementation during eight hours of acclimatization to nitrogen dilution hypoxia. They found, with hypocapnic hypoxia, the ventilation-P_{CO_2} relationship shifted more to lower values of P_{CO_2} (-8 torr) than with normocapnic hypoxia (-4 torr). The relatively large changes which occurred during brief hypoxia probably reflected their data analysis. They arbitrarily took values of P_{CO_2} at ventilation of 15 L/min $\cdot$ m^2. Because the slope of the ventilation-P_{CO_2} line increases during hypoxia their differences are magnified. However, both the results of Eger et al. and our own results from the present study indicate that CO_2 supplementation interferes with the process of ventilatory adaptation to high altitude.

c) Ventilatory Responses to Isocapnic Hypoxia

Ventilatory response to isocapnic hypoxia increases with time during high altitude exposure (Cruz and Hurtado, 1970, Forster et al. 1971, Michel

and Milledge, 1963, Reed and Kellogg, 1960). We have also made the same observation in the group without CO_2, which correlated with the shift of the curve that relates ventilation-P_{CO_2}. Thus, it appears that both peripheral and central chemoreceptors influenced the process of ventilatory acclimatization to high altitude. In contrast, no significant changes with time in the ventilatory response to isocapnic hypoxia was observed in the CO_2 group. When arterial pH remains similar at altitude as well as at sea level by CO_2 inhalation, no difference in the ventilatory response to hypoxia has been observed (Gabel and Weiskopf, 1975). Since no shift was measured also in the ventilation-CO_2 curve in the CO_2 group, prevention of hypocapnia did not allow the chemoreceptors to be altered. Thus, no ventilatory acclimatization took place.

Mechanisms

Severinghaus et al. (1963) originally proposed that the initial respiratory alkalosis with high altitude exposure, along with its moderating effect on ventilation, was progressively reduced by restoring the alkaline cerebrospinal fluid pH toward normal sea level values. Subsequently, however, measurements in man (Dempsey, Forster, and de Pico, 1974; Dempsey et al., 1975; Forster, Dempsey and Chosy, 1975; Weiskopf, Gabel, and Fenel, 1976) and animals (Burean and Bouberot, 1975; Cruz et al., 1978; Orr et al., 1975) during altitude acclimatization did not show such normalization of the spinal fluid pH. In addition, recent evidence suggests that the local central nervous system tissue $[H^+]$ is more acid than the spinal fluid during acclimatization to hypoxia (Davies, 1978; Fenel, Gabel and Wolfe, 1979). Our present study does not report blood or spinal fluid pH

values. But the results are compatible with the concept that CO_2 breathing probably avoided alkalinization of the central and peripheral chemoreceptors allowing the hypoxic stimulus to be fully effective at the outset of the altitude exposure.

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TABLE 1. Ventilatory measurements at rest at low altitude and with or without CO_2 addition at high altitude.*

4 Subjects with CO_2

Time at Altitude	P_B (mm Hg)	P_AO_2 (mm Hg)	P_ACO_2 (mm Hg)
Control	760	105 ± 2	39 ± 1
3 h.	465	59 ± 1	
27 h.	465	62 ± 2	43 ± 2
51 h.	440	57 ± 2	42 ± 1
75 h.	440	55 ± 2	40 ± 1

4 Subjects without CO_2

Control	760	108 ± 1	39 ± 1
3 h.	492	55 ± 1	40 ± 1
27 h.	492	58 ± 2	37 ± 1
51 h.	492	59 ± 1	35 ± 1
75 h.	475	61 ± 2	33 ± 3

*Given are mean values and one standard error of the mean.

TABLE 2. Mean value and one standard error of ventilation ($\dot{V}_{E_{BTPS}}$) and oxygen uptake ($\dot{V}O_2$) in liters/minute at sea level and high altitude, in subjects seated on a bicycle ergometer at rest and during two 6-minute exercise stints.

Time at Altitude	Work Load in Kg/m/min					
	Rest		300		600	
	$\dot{V}_E$	$\dot{V}_{O_2}$	$\dot{V}_E$	$\dot{V}O_2$	$\dot{V}_E$	$\dot{V}_{O_2}$
	4 subjects with CO_2					
Control	12 ± 2.7	.36 ± .05	24 ± 0.8	.96 ± .05	41 ± 1.8	1.56 ± .06
8 h.	20 ± 1.2	.40 ± .04	46 ± 1.2	.94 ± .02	80 ± 6.2	1.58 ± .05
32 h.	23 ± 1.1	.38 ± .04	51 ± 1.2	.96 ± .05	91 ± 7.9	1.60 ± .08
56 h.	23 ± 1.0	.40 ± .04	52 ± 2.1	1.00 ± .04	98 ± 8.5	1.75 ± .04
100 h.	22 ± 0.6	.38 ± .03	56 ± 3.2	1.05 ± .02	101 ± 9.5	1.72 ± .04
	4 subjects without CO_2					
Control	12 ± 1.2	.32 ± .01	27 ± 2.8	.92 ± .03	44 ± 2.6	1.56 ± .05
8 h.	15 ± 1.3	.39 ± .03	32 ± 2.3	.98 ± .03	64 ± 9.5	1.62 ± .06
32 h.	18 ± 1.9	.44 ± .02	38 ± 3.2	1.06 ± .02	65 ± 8.3	1.68 ± .05
56 h.	19 ± 2.6	.38 ± .01	41 ± 6.4	1.02 ± .02	69 ± 8.9	1.60 ± .03
100 h.*	22 ± 5.4	.35 ± .02	50 ± 8.8	1.02 ± .02	88 ±17.0	1.64 ± .04

*n = 3.

LEGENDS

Figure 1 Measurements of resting ventilation made each morning during 75 hours of exposure to simulated high altitude. Solid circles indicate mean values in four subjects given supplemental CO_2 at high altitude. All measurements at high altitude were greater than the sea level measurement. Open circles indicate mean values in four subjects without CO_2 addition. At high altitude, only the measurement at 75 hours differed from the sea level control. One standard error of the mean is indicated.

Figure 2 Measurements of resting and exercise ventilation (made in the afternoons with the subjects seated on the bicycle ergometer) during 100 hours of exposure to simulated high altitude. Symbols represent interpolated ventilations at 3 standard metabolic rates as explained in the results. Closed circles represent the group with CO_2 and the open circles represent the group without CO_2.

Figure 3 Measurements relating to control of breathing made each morning during 75 hours exposure to simulated high altitude.
Top: Hypoxic ventilatory responses ("A" value) for the group with CO_2 (solid circles) show no change. The group without CO_2 (open circles) show a progressive increase. The values at 75 hours are different between the two groups.
Middle: The ventilatory responses to CO_2 ("S" value) were not altered with high altitude exposure in either group.
At 75 hours exposure the values differed between the groups.

Bottom: The shift to a lower PCO_2 of the line relating ventilation to P_ACO_2 as measured by the intercept "B" occurred only in group without CO_2. At 75 hours, the two groups were different.

Figure 4 Relationship of the intercept "B" to P_ACO_2 in each of the four subjects without CO_2 at sea level and during 75 hours of high altitude exposure.

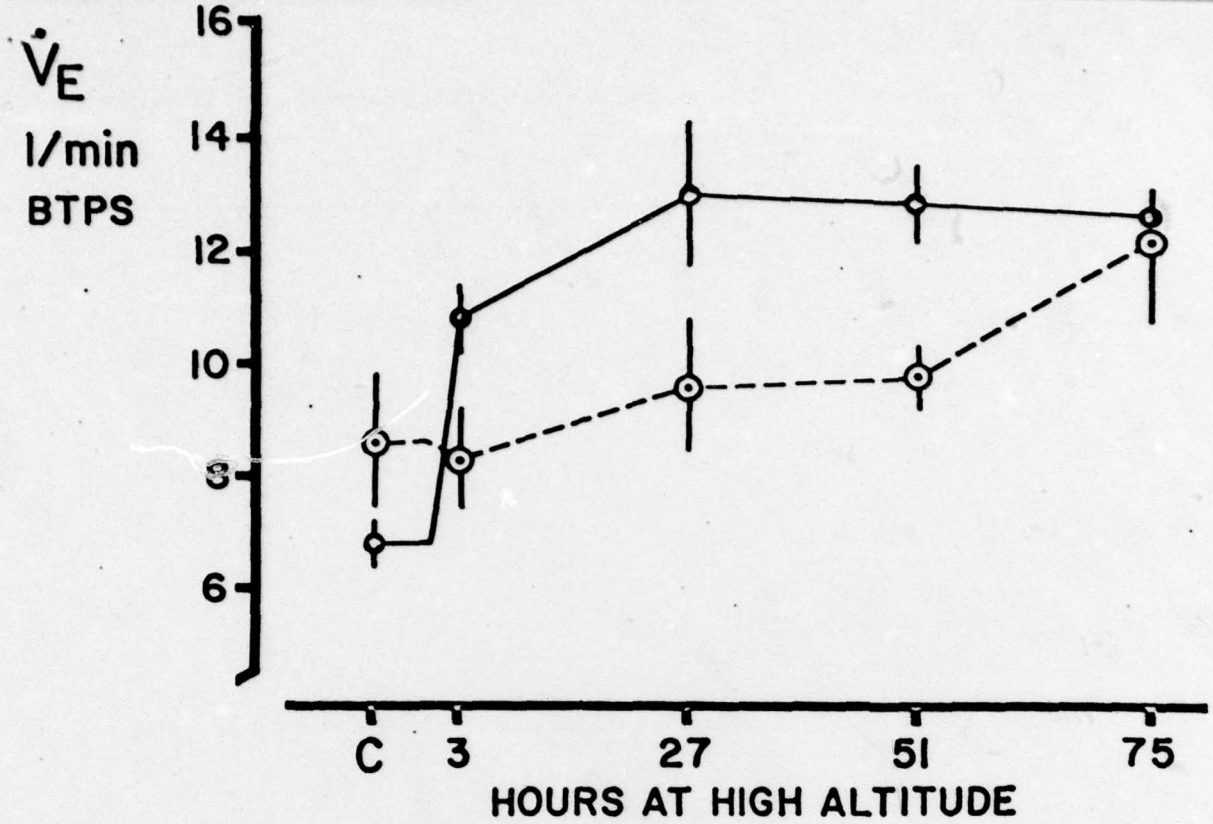
$\dot{V}_E$
l/min
BTPS
16
14
12
10
8
6
C
3
27
51
75
HOURS AT HIGH ALTITUDE

Figure 1

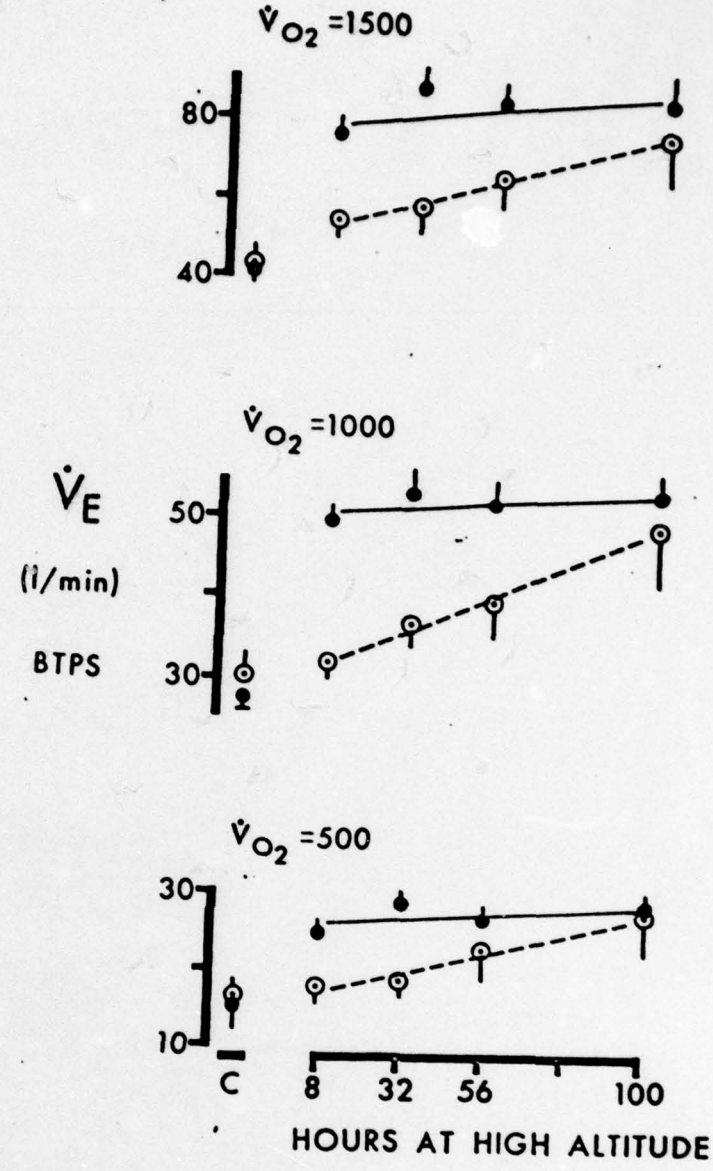
$\dot{V}_{O_2}$ =1500
80
40
$\dot{V}_{O_2}$ =1000
$\dot{V}_E$
(l/min)
BTPS
50
30
$\dot{V}_{O_2}$ =500
30
10
C
8
32
56
100
HOURS AT HIGH ALTITUDE

Figure 2

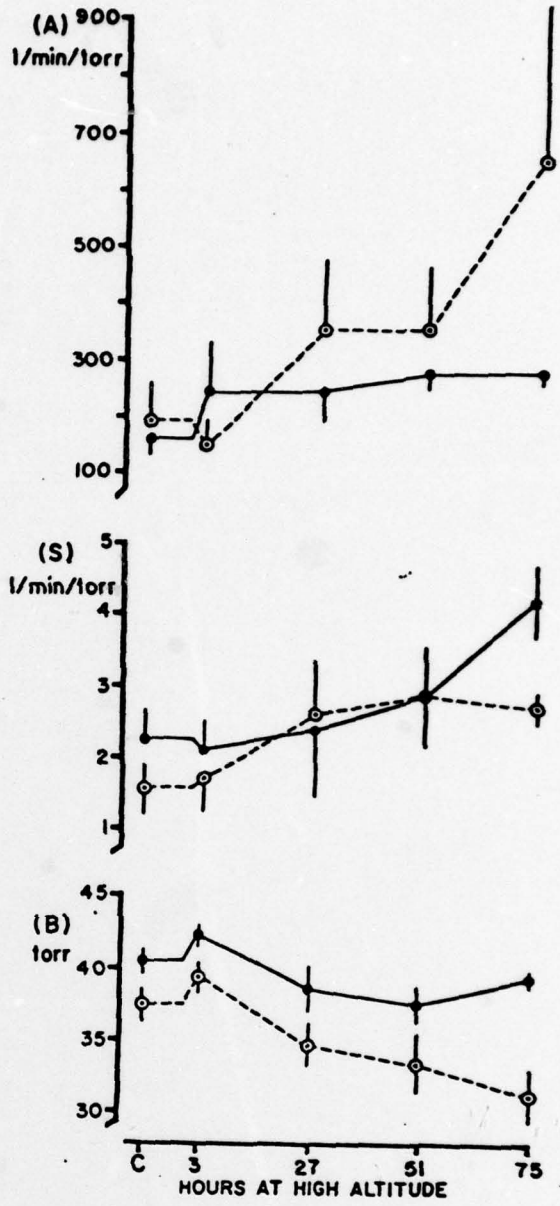
(A)
l/min/torr
900
700
500
300
100
(S)
l/min/torr
5
4
3
2
1
(B)
torr
45
40
35
30
C
3
27
51
75
HOURS AT HIGH ALTITUDE

Figure 3

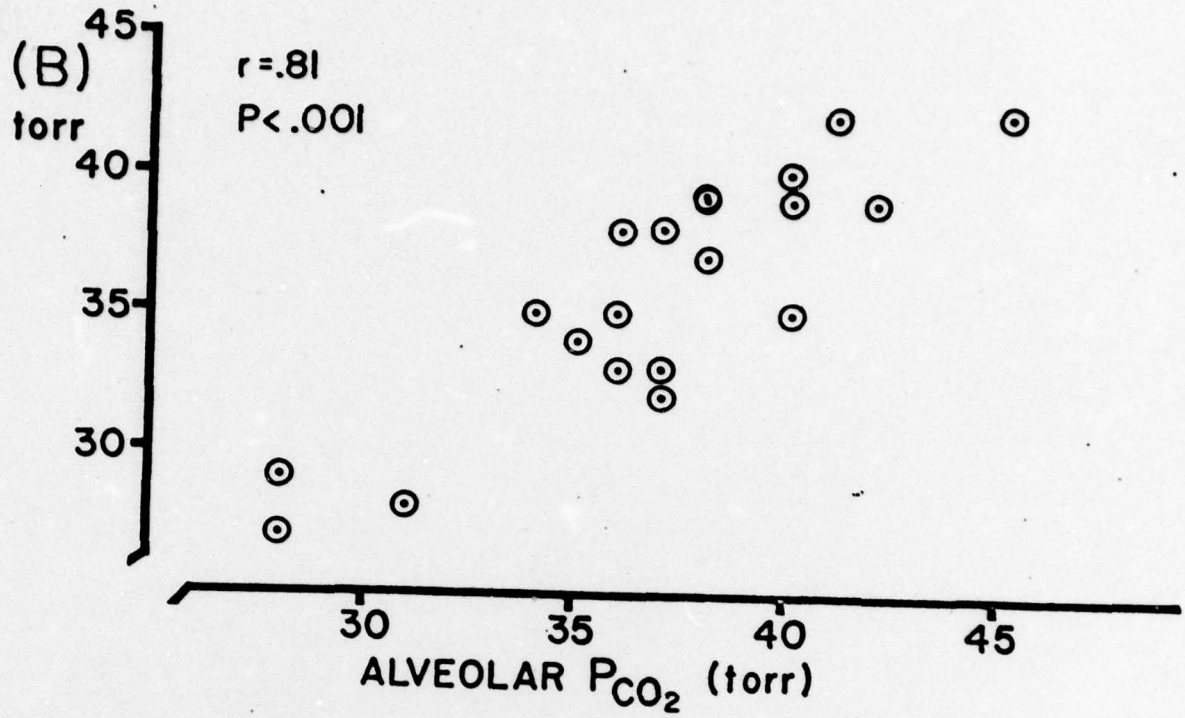

Figure 4

The views, opinions, and/or findings contained in this report are those of the author and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in this study after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.